



US009011884B2

(12) **United States Patent**
Constant et al.

(10) **Patent No.:** **US 9,011,884 B2**
(45) **Date of Patent:** **Apr. 21, 2015**

(54) **EMBOLIC DEVICES**

(71) Applicant: **MicroVention, Inc.**, Tustin, CA (US)

(72) Inventors: **Michael Constant**, Mission Viejo, CA (US); **Edward Michael Keeley**, Huntington Beach, CA (US); **Joshua Garretson**, San Diego, CA (US); **Gregory M. Cruise**, Rancho Santa Margarita, CA (US)

(73) Assignee: **MicroVention, Inc.**, Tustin, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 185 days.

(21) Appl. No.: **13/865,068**

(22) Filed: **Apr. 17, 2013**

(65) **Prior Publication Data**

US 2013/0302251 A1 Nov. 14, 2013

Related U.S. Application Data

(60) Provisional application No. 61/635,190, filed on Apr. 18, 2012.

(51) **Int. Cl.**

A61K 9/00 (2006.01)
A61K 49/04 (2006.01)
A61K 49/12 (2006.01)
A61L 31/04 (2006.01)
A61L 31/14 (2006.01)
A61L 31/18 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 49/0404** (2013.01); **A61K 49/126** (2013.01); **A61L 31/048** (2013.01); **A61L 31/145** (2013.01); **A61L 31/18** (2013.01); **A61L 2430/36** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,549,624	A	8/1996	Mirigian et al.
6,187,024	B1	2/2001	Boock et al.
6,312,421	B1	11/2001	Boock et al.
6,602,261	B2	8/2003	Greene et al.
7,422,569	B2	9/2008	Wilson et al.
2003/0232895	A1	12/2003	Omidian et al.
2005/0196426	A1	9/2005	Cruise et al.
2007/0299464	A1	12/2007	Cruise et al.
2008/0089940	A1	4/2008	Omdian et al.
2009/0164013	A1	6/2009	Cruise et al.
2010/0249913	A1	9/2010	Datta et al.
2011/0212178	A1	9/2011	Constant et al.

FOREIGN PATENT DOCUMENTS

WO 2013/158781 10/2013

OTHER PUBLICATIONS

International Search Report mailed on Aug. 14, 2013 for PCT/US2013/037007.

Primary Examiner — James Rogers

(74) *Attorney, Agent, or Firm* — K&L Gates LLP; Louis C. Cullman; Brian J. Novak

(57) **ABSTRACT**

Described herein are apparatus, compositions, systems and methods for occluding vascular structures and vascular malformations with radiopaque hydrogel filaments. The filaments can contain no support members and can be CT and MR compatible. Methods of forming such filaments are also disclosed.

22 Claims, 3 Drawing Sheets

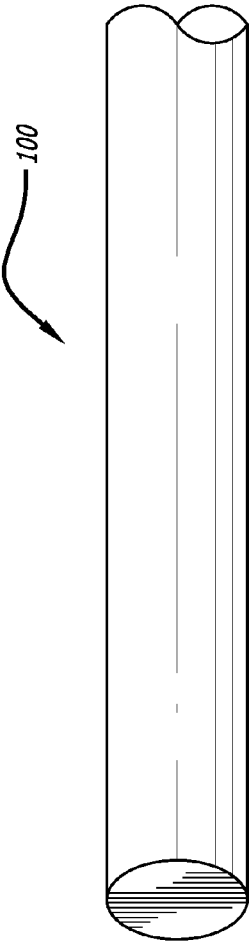


FIG. 1

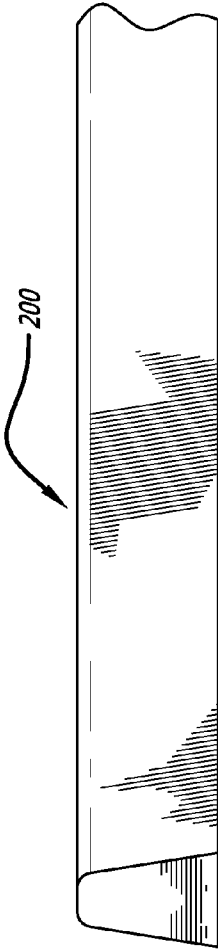


FIG. 2

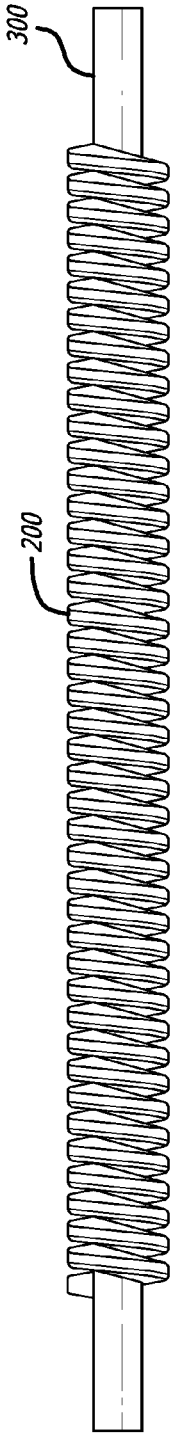
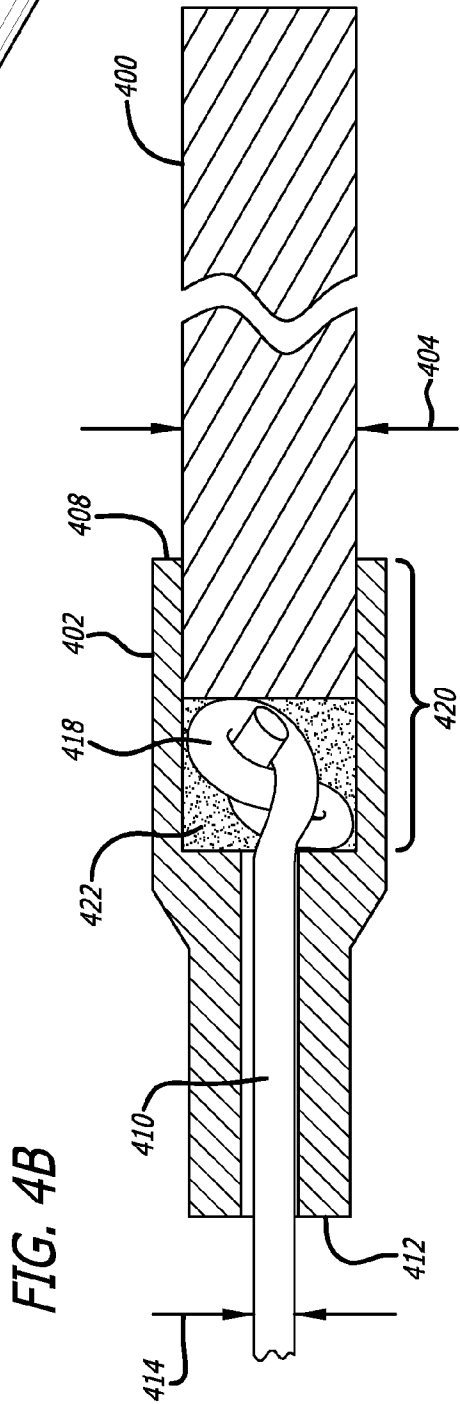
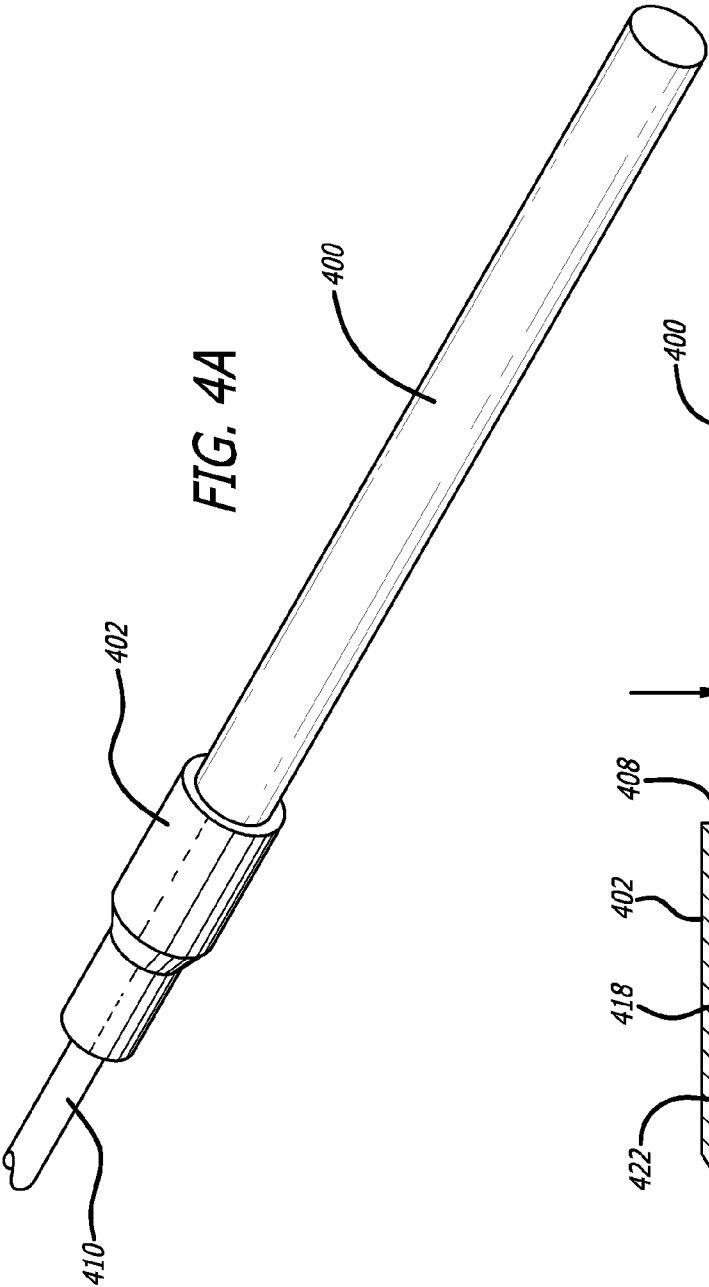
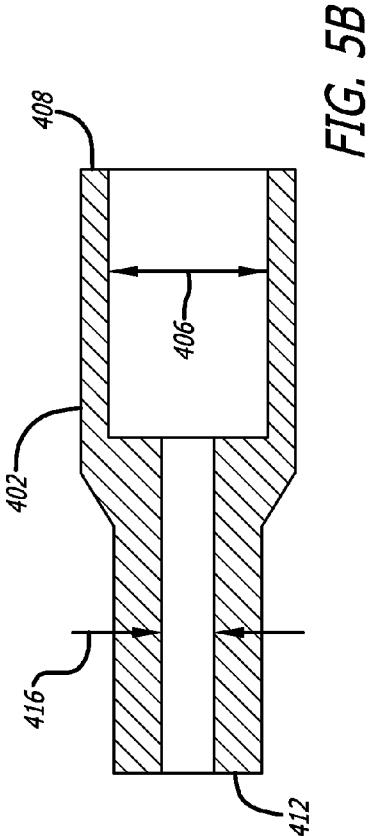
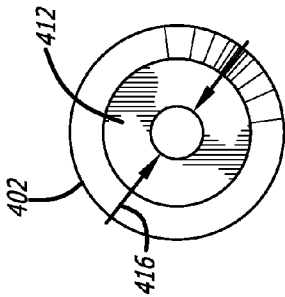
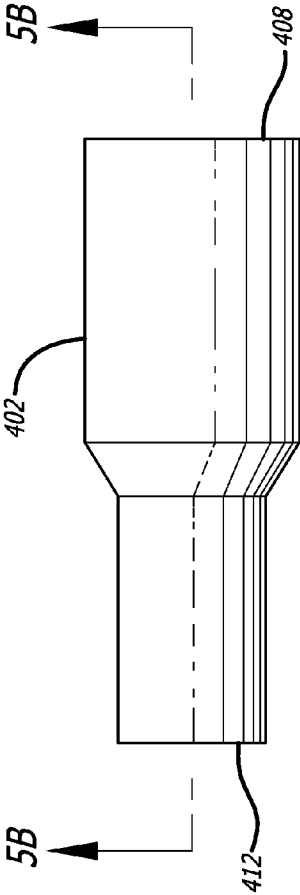


FIG. 3





1

EMBOLIC DEVICES**CROSS REFERENCE TO RELATED APPLICATIONS**

The present application claims the benefit of U.S. Provisional Patent Application No. 61/635,190 filed Apr. 18, 2012, the entire contents of which are hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates generally to implantable hydrogel filaments and medical treatment methods using the hydrogel filaments, wherein the filaments can be visualized using medically relevant imaging techniques.

BACKGROUND

Despite the number of vascular coil devices available, there exists a clinical need for polymer filament devices that can be deployed using standard microcatheters and catheters to treat sites in the peripheral vasculature. Of particular clinical need is a polymer filament device that can be deployed using standard medical techniques through standard microcatheters and catheters to treat sites in the neuro and peripheral vasculature and can be compatible with various medical imaging techniques such as computed tomography imaging.

SUMMARY

Described herein generally are hydrogels and hydrogel filaments, methods of forming those filaments, and medical treatment methods using the hydrogel filaments. The hydrogel filaments possess enough structural strength not to require metallic support members when deployed in vivo through a vessel. The filaments can also be opacified in order to visualize the filaments using medically relevant imaging techniques.

In one embodiment, hydrogels are described for implantation comprising a shapeable polymeric filament formed from a reaction product of at least one multifunctional, low molecular weight, ethylenically unsaturated macromer; at least one ethylenically unsaturated monomer; and comprising at least one visualization element, wherein the polymeric filament includes no metallic support members. In some embodiments, the hydrogels can be further formed with an ethylenically unsaturated cross-linker, which can be multifunctional.

In another embodiment, hydrogels for implantation are described comprising a shapeable polymeric filament formed from a combination of precursors comprising at least one low molecular weight, ethylenically unsaturated macromer; at least one ethylenically unsaturated monomer; and a crosslinker; and comprising at least one visualization agent; and wherein the hydrogel includes no metal support members.

In some embodiments, the at least one ethylenically unsaturated monomer can be t-butyl acrylamide, hydroxyethyl methacrylate or a combination of both. The difunctional, macromer may be trimethylolpropane ethoxylate triacrylamide and may have a molecular weight of about 900 g/mol. In some embodiments, the crosslinker can be N,N'-methylenebisacrylamide.

In other embodiments, the hydrogels can reduce beam hardening artifacts when imaged using computed tomography. A visualization element can be a soluble or insoluble

2

opacification compound, gadolinium, iodine, barium sulfate, superparamagnetic iron oxide particles, or a combination thereof. In another embodiment, a visualization element can be barium sulfate. For example, barium sulfate can be useful for fluoroscopic and CT visibility. For MR visibility, the filaments can be opacified with gadolinium or superparamagnetic iron oxide particles.

Polymer filaments can be sized with virtually any diameter. In some embodiments, polymer filaments can be sized to deploy, and optionally reposition, through microcatheters with inner diameters ranging from about 0.002 inches to about 0.045 inches. In another embodiment, polymer filaments can be sized to deploy, and optionally reposition, through 2 Fr, 3 Fr, 4 Fr, 5 Fr, 6 Fr, 7 Fr, 8 Fr, 9 Fr, 10 Fr, and larger catheters. The polymer filaments generally can have diameters of less than about 0.002 inches or less than about 0.100 inches.

In one embodiment, polymer filaments can be delivered with a saline flush through a microcatheter or catheter to the vasculature. In another embodiment, polymer filaments can be delivered using a guide wire or coil pusher through the microcatheter or catheter to the vasculature. In some embodiments, polymer filaments can be releasably attached to a delivery pusher. After repositioning, if desired, polymer filaments can be detached from the delivery pusher and the delivery pusher can be subsequently removed.

In one embodiment, polymer filaments can be biostable and not susceptible to degradation in a physiological environment. Alternatively in another embodiment, polymer filaments can be biodegradable and controllably dissolve in a physiological environment.

In one embodiment, significant fluid uptake by a polymer filament may occur and a large increase in the volume of the polymer filament may occur in a physiological environment. In another embodiment, only a small amount of fluid uptake by a polymer filament may occur and only a small increase in the volume of the polymer filament may occur in a physiological environment. In yet another environment, no fluid uptake by a polymer filament may occur and the volume of the polymer filament may remain unchanged in a physiological environment.

Also described herein are methods of forming hydrogels comprising: a. preparing a polymerization solution comprising a trimethylolpropane ethoxylate triacrylamide 900 macromer; at least one ethylenically unsaturated monomer; and at least one visualization element in a solvent; b. polymerizing the polymerization solution to create a polymerized hydrogel; and c. drying the hydrogel filament. In another embodiment, step b can further comprise polymerizing the polymerization solution in a tube thereby creating a polymerized hydrogel filament having the shape of the internal volume of the tube. In another embodiment, the tube may be wrapped around a mandrel of virtually any shape before filling with the polymerization solution to impart a three dimensional shape to the resulting polymerized hydrogel filament.

The solvent can be any that dissolves the macromers and monomers. In one embodiment, isopropanol, ethanol, water, dichloromethane, dimethyl formamide, acetone, butanol, or a combination thereof can be used as a solvent.

In some embodiments, hydrogel filaments can consist essentially of about 27% w/w trimethylolpropane ethoxylate triacrylamide 900, about 8% w/w t-butyl acrylamide, about 2% hydroxyethyl methacrylate, about 1% w/w N,N'-methylenebisacrylamide, about 66% barium sulfate, and about <1% 2,2'-azobisisobutyronitrile.

In some embodiments, hydrogel filaments can consist essentially of about 30% w/w trimethylolpropane ethoxylate

triacylamide 900, about 6% w/w t-butyl acrylamide, about 2% hydroxyethyl methacrylate, about 1% w/w N,N-methylenebisacrylamide, about 61% barium sulfate, and about <1% 2,2'-azobisisobutyronitrile.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a cylindrical hydrogel filament according to an embodiment of the present description.

FIG. 2 illustrates a trapezoidal hydrogel filament according to an embodiment of the present description.

FIG. 3 illustrates the hydrogel filament of FIG. 2 wrapped around a mandrel to form a coil.

FIG. 4A illustrates a hydrogel filament attached to a coupler. FIG. 4B illustrates a hydrogel filament and an insertion filament attached to a coupler using glue and a knot in the insertion filament.

FIG. 5A illustrates a side view of a coupler. FIG. 5B illustrates a cross-sectional view of the coupler of FIG. 5A. FIG. 5C is a front view of a coupler.

DETAILED DESCRIPTION

Described herein generally are hydrogel filaments and medical treatment methods using the hydrogel filaments. Methods of forming the hydrogel filaments are also described herein, including methods of making the hydrogel filaments. Generally, the hydrogel filaments can possess enough structural column strength so as to not require metallic support members. The filaments can also be opacified in order to visualize the filaments using medically relevant imaging techniques.

The hydrogel filaments and associated methods can be for occluding structures and malformations resulting from one or more neuro, cerebral and/or peripheral vascular diseases. Further, the hydrogel filaments include one or more visualization agents, for example, radiopaque elements or fillers.

Generally, the hydrogel filaments can be deployed within the vasculature using standard practices and microcatheters/catheters to occlude blood flow. The polymer filaments can be prepared by polymerizing a solution of monomers, macromers, and optionally, cross-linkers. For fluoroscopic visibility, the filaments can be opacified with any compound or substance that can be used to visualize the filaments. For example, the filaments can be opacified with iodine, barium sulfate, or metallic powders. For computed tomography imaging, the filaments can be opacified with iodine or barium sulfate. For magnetic resonance imaging, the filaments can be opacified with gadolinium or superparamagnetic iron oxide particles.

As used herein, the term "macromer" includes large molecules containing at least one active polymerization site or binding site. Macromers can have a larger molecular weight than monomers such as at least about 100 grams/mole, about 200 grams/mole, about 500 grams/mole or about 900 grams/mole. For example, an acrylamide monomer can have a molecular weight of about 71.08 grams/mole whereas a trimethylolpropane ethoxylate triacrylamide macromer can have a molecular weight of about 900 grams/mole. Some macromers can be shapeable and non-ionic.

As used herein, the term "non-resorbable" includes a material that cannot be readily and/or substantially degraded and/or absorbed by bodily tissues.

As used herein, the term "ethylenically unsaturated" includes a chemical entity (e.g., a macromer, monomer or polymer) containing at least one carbon-carbon double bond.

Some hydrogel filaments described herein may have no metal support members to aid in supporting the filaments before, during and after implantation. The filaments can be delivered through a catheter or microcatheter using a pusher or guidewire or even a liquid flush (e.g. saline). The hydrogel filaments may have sufficient column strength to alleviate the need for metal support member, yet soft and flexible enough to navigate through vasculature. However, unlike filaments in the art, the hydrogel filaments described herein can have sufficient column strength to be advanced out of a catheter or microcatheter device by pushing with a pusher or guidewire.

Filaments described herein can be shapeable in that they can be formed into a particular shape and hold that shape for a predetermined amount of time once hydrated. For example, the time can be about 10 seconds, 30 second, 1 minute, 5 minutes, 15 minutes 30 minutes or 1 hour. For example the filaments described herein can be formed around a mandrel or wrapped around one once formed to establish a secondary shape for the filament.

Filaments described herein may be formed from polymerization solutions comprising such components as one or more solvent(s), one or more macromer(s), one or more monomer(s), one or more cross-linker(s), one or more visualization agent(s), and one or more initiator(s). Some components may be optional.

The solvent's function can be to dissolve at least part of the macromers, monomers, cross-linkers, initiators, and soluble visualization agents needed to form a particular filament. In some instances, all of the components may be completely dissolved in the solvent. In other embodiments, the visualization agent or agents may or may not dissolve in the solvent. If a liquid monomer (e.g. 2-hydroxyethyl methacrylate) is used, a solvent may not be necessary. The solvent, if necessary, can be selected based on the solubility of the components of the polymerization solution. Solvents can include isopropanol, ethanol, water, dichloromethane, dimethyl formamide, butanol, and acetone. Any number of solvents can be utilized and a skilled artisan can match a solvent to a particular polymer system.

Solvent concentrations can be from about 5% w/w to about 80% w/w, about 30% w/w to about 60% w/w, about 40% w/w to about 50% w/w, about 5% w/w, about 10% w/w, 20% w/w, 30% w/w, 40% w/w, 50% w/w, 60% w/w, 70% w/w, 80% w/w, 90% w/w of the polymerization solution, or any percentage or range of percentages within those listed. In one embodiment, the solvent can make up about 15% w/w of the polymerization solution.

The polymerization solutions may include at least one macromer. A function of the macromer can be to impart desired mechanical properties to the filaments as well as provide a bulk structural framework for the filament. Macromers with solubility in solvents and functional groups amenable to modifications can be used in some embodiments. Polyethers, due to their solubility in a variety of solvents, their availability in a variety of forms, and their terminal groups amenable to functionalization, can be utilized herein. While poly(ethylene glycol), poly(propylene glycol), and poly(tetramethylene oxide) can be suitable polyethers, a preferred macromer can be ethoxylated trimethylol propane having a low molecular weight and the presence of three hydroxyl groups. Non-polyether polymers with functional groups available for modification, such as poly(vinyl alcohol), can also be utilized as macromers. In one embodiment, the macromer may be trimethylolpropane ethoxylate triacrylamide. In another embodiment the macromer can be ethoxylated trimethylolpropane triacrylamide with a molecular weight of about 900 g/mole.

Macromer concentrations can range from about 10% w/w to about 40% w/w, about 20% w/w to about 35% w/w, about 12% w/w to about 20% w/w, about 22% w/w to about 24% w/w, or any percentage or range of percentages within those listed of the polymerization solution. In one embodiment, the macromer concentration can be about 23% w/w or about 25% w/w of the polymerization solution.

The molecular weight of the macromer can change the resulting hydrogel's mechanical properties, in some cases to a large extent. Smaller molecular weights can result in filaments with sufficient column strength to be pushed through microcatheters and catheters. Larger molecular weights may result in filaments that can require more effort to be pushed through microcatheters and catheters. The macromers described herein can have a molecular weight ranging from about 100 g/mole to about 5,000 g/mole, about 250 g/mole to about 2,500 g/mole, about 400 g/mole to about 1,200 g/mole or any molecular weight or range of molecular weights within those listed. In one embodiment, molecular weight can be about 900 g/mole.

Any functional groups associated with the macromers described can be derivatized. The functional groups of the macromers can be derivatized to impart ethylenically unsaturated moieties allowing free radical polymerization of the hydrogel. Functionalities for free radical polymerization can include acrylates, methacrylates, acrylamides, vinyl groups, derivatives and/or combinations thereof. Alternatively, other reactive chemistries can be employed to polymerize the hydrogel, for example, nucleophile/N-hydroxysuccinimide esters, vinyl sulfone/acrylate or maleimide/acrylate. In one embodiment, a preferred functional group of the macromer can be an acrylate.

Biostability, non restorability, and/or biodegradation can be imparted to hydrogels described by altering the synthetic route to derivatize macromer functional groups. If biostability and/or non restorability are desired, a linkage with stability in the physiological environment can be utilized. The biostable linkage can be an amide. The macromer hydroxyl group(s) can be converted to an amino group followed by reaction with acryloyl chloride to form an acrylamide group. If biodegradation is desired, linkages susceptible to breakage in a physiological environment can be utilized. Biodegradable linkages can include esters, polyesters, and amino acid sequences degradable by enzymes.

Monomers can also be used to aid in polymerization of the hydrogel and impart specific mechanical properties to the resulting hydrogel. In one embodiment, the monomers may not be sensitive to pH. The monomers can be any molecule with a single functionality to incorporate into the resulting hydrogel and a structure conducive to the desired mechanical property. The monomers can be, for example, hydrophobic thereby imparting column strength to the resulting hydrogel. Also or in addition, the monomer can have a bulky structure further imparting column strength to the resulting hydrogel. Internal hydrogen bonding within the monomer can impart increasing tensile strength to the resulting polymer. Monomers can include t-butyl acrylamide, 2-hydroxyethyl methacrylate, and derivatives thereof. Concentrations of monomers can range from about 2% to about 30% w/w, about 3% w/w to about 12% w/w about 5% w/w to about 10% w/w of the polymerization solution, or any percentage or range of percentages within those listed. In some embodiments, the monomer can be t-butyl acrylamide and can be present at about 5% w/w or about 6% w/w. In some embodiments the monomer can be hydroxyethyl methacrylate and can be

present at about 2% w/w. In other embodiments, the monomer can be a combination of t-butyl acrylamide and hydroxyethyl methacrylate.

In one embodiment, depending on the monomers chosen for a particular hydrogel, significant fluid uptake by the polymer filament can occur and a large increase in the volume of the polymer filaments can occur in a physiological environment. In another embodiment, monomers chosen may allow only a small amount of fluid uptake by the polymer filament and only a small increase in the volume of the polymer filament may occur in a physiological environment. In yet another environment, monomers chosen can prevent fluid uptake by the polymer filament and the volume of the polymer filaments can remain unchanged in a physiological environment.

Crosslinker(s), although optional, can impart desired mechanical properties to the hydrogels. The crosslinker can be a multifunctional crosslinker. The crosslinker can be any molecule with at least two functionalities to incorporate into the resulting hydrogel and a structure conducive to the desired mechanical property. One example crosslinker can be N,N-methylenebisacrylamide. Concentrations of the crosslinker can be less than about 2% w/w, less than about 1% w/w, less than about 0.5% w/w, or less than about 0.1% w/w of the polymerization solution. In some embodiments, the concentration of the crosslinker is about 0.2% w/w, about 0.5% w/w, about 1% w/w, or about 2% w/w. The crosslinker can be at any percentage or range of percentages within those listed. In one embodiment, the concentration of crosslinker can be about 0.5% w/w.

In one embodiment, polymerization can be initiated by azobisisobutyronitrile (AIBN) or a water soluble AIBN derivative. Other initiators useful according to the present description include N,N,N',N'-tetramethylethylenediamine, ammonium persulfate, benzoyl peroxides, 2,2'-azobis(2-methylpropionamide) dihydrochloride, and derivatives and/or combinations thereof, including azobisisobutyronitriles. Azobisisobutyronitrile can be the initiator. Concentrations of the initiator can be less than about 5% w/w or about 1% w/w of the prepolymer solution.

A function of the initiator may be to start the polymerization of the polymerizable components of the prepolymer or polymerization solution. The prepolymer solution can be polymerized by reduction-oxidation, radiation, heat, or any other method known in the art. Radiation cross-linking of the pre-polymer solution can be achieved with ultraviolet light or visible light with suitable initiators or ionizing radiation (for example, electron beam or gamma ray) without initiators. Cross-linking can be achieved by application of heat, either by conventionally heating the solution using a heat source such as a heating well, or by application of infrared light to the prepolymer solution.

Visualization agents can also be added to the hydrogels described herein. Since metallic support members are not used in conjunction with the presently described hydrogel filaments, visualization agents can be added to the hydrogels to impart visualization. Generally, in the art, metallic support members aid in the visualization of embolic devices. Here, this is not the case. The visualization agents impart visibility of the resulting hydrogel when imaged using a medically relevant imaging technique such as fluoroscopy, computed tomography, or magnetic resonance techniques. However, in some embodiments, metallic support members can be used at least in or on portions of the hydrogel filament.

Visualization of the hydrogel filaments under fluoroscopy can be imparted by the incorporation of solid particles of radiopaque materials including barium, bismuth, tantalum,

platinum, gold, and other heavy nuclei species into the hydrogel or by polymerization of iodine or other molecules into the hydrogel structure. A preferred visualization agent for fluoroscopy can be barium sulfate. Visualization of the hydrogel filaments under computed tomography imaging can be imparted by incorporation of solid particles of barium or bismuth.

Heavy metals visible under fluoroscopy can sometimes result in beam hardening artifacts that preclude the usefulness of computed tomography imaging for medical purposes. A visualization agent for computed tomography imaging may be barium sulfate. Concentrations of barium sulfate may range from about 30% w/w to about 90% w/w, about 40% w/w to about 80% w/w, about 60% w/w to about 70% w/w of the polymerization solution or any percentage or range of percentages within those listed. In one embodiment, barium sulfate can be present at about 50% w/w to about 60% w/w. Such concentrations of barium sulfate can render the hydrogel filaments visible using fluoroscopic and computed tomography imaging.

Visualization of the hydrogel under magnetic resonance imaging can be imparted by the incorporation of solid particles of superparamagnetic iron oxide or gadolinium molecules polymerized into the hydrogel structure. A visualization agent for magnetic resonance may be superparamagnetic iron oxide with a particle size of about 10 microns. Concentrations of superparamagnetic iron oxide particles to render the hydrogel visible using magnetic resonance imaging can range from about 0.01% w/w to about 2% w/w, about 0.05% w/w to about 0.75% w/w, about 0.1% w/w to about 1% w/w of the polymerization solution or any percentage or range of percentages within those listed.

In one embodiment, a hydrogel filament can be formed from a prepolymer solution containing a macromer, monomers, a crosslinker, an initiator and a visualization agent. In another embodiment, the macromer, monomers, crosslinker, and initiator can be dissolved in a solvent. After dissolution of these components, an insoluble visualization agent can be suspended in the prepolymer solution. Mixing of the prepolymer solution containing an insoluble visualization agent with a homogenizer may aid the suspension of the insoluble visualization agent.

In one embodiment, a hydrogel filament formed from an above prepolymer solution can include about 27% w/w trimethylolpropane ethoxylate triacrylamide 900, about 6% w/w t-butyl acrylamide, about 2% hydroxyethyl methacrylate, about 0.5% w/w N,N-methylenebisacrylamide, about 64% barium sulfate, and less than about 0.5% azobisisobutyronitrile.

In another embodiment, a hydrogel filament formed from an above prepolymer solution can include about 30% w/w trimethylolpropane ethoxylate triacrylamide 900, about 6% w/w t-butyl acrylamide, about 2% hydroxyethyl methacrylate, about 0.75% w/w N,N-methylenebisacrylamide, about 48% barium sulfate, and less than about 0.5% azobisisobutyronitrile.

The hydrogel filaments can have many characteristic properties one of which is bending resistance. Bending resistance can be based on factors such as diameter and/or hydration. The filaments can have a dry bending resistance of about 0.5 mg to about 1000 mg, about 1 mg to about 500 mg, about 2 mg to about 250 mg, about 5 mg to about 500 mg, about 10 mg to about 100 mg, about 0.49 mg, about 1.11 mg, about 6.67 mg, about 9.04 mg, about 10.56 mg, about 19.07 mg, about 36.39 mg, about 63.68 mg, about 128.21 mg, about 1,021.20 mg, or any bending resistance or range of bending resistances within those listed. The filaments can also have a hydrated bending

resistance of about 0.5 mg to about 1000 mg, about 1 mg to about 500 mg, about 2 mg to about 250 mg, about 5 mg to about 500 mg, about 10 mg to about 100 mg, about 0.28 mg, about 4.73 mg, about 7.78 mg, about 8.62 mg, about 17.38 mg, about 29.40 mg, about 59.10 mg, about 121.58 mg, about 860.25 mg, or any bending resistance or range of bending resistances within those listed.

Another filament characteristic can be average ultimate tensile strength. The hydrogel filaments described herein can have an average ultimate tensile strength of about 0.03 lbf to about 2 lbf, about 0.08 lbf to about 0.20 lbf, about 0.52 lbf to about 0.65 lbf, about 0.1 lbf to about 10 lbf, about 1 lbf to about 15 lbf, about 0.05 lbf to about 20 lbf, about 0.07 lbf to about 2 lbf, about 0.03 lbf to about 0.1 lbf or any average ultimate tensile strength or range of average ultimate tensile strengths within those listed.

Methods of preparing hydrogels and/or hydrogel filaments are also described. The prepolymer solution can be prepared by dissolving at least one macromer, at least one monomer, optionally a multifunctional cross-linker, and optionally an initiator in a solvent, and adding a visualization agent to the prepolymer solution. A visualization agent can be suspended in the polymerization solution or can be dissolved in the prepolymer solution. In other embodiments, the visualization agent can be soluble in the solvent. Mixing of the polymerization solution containing an insoluble visualization agent with a homogenizer aids in suspension of the insoluble visualization agent.

Then, the polymerization solution can be injected into tubing with an inner diameter ranging from about 0.006 inches to about 0.080 inches and incubated for several hours in boiling water, for example, at 100° C., and subsequently overnight at 80° C. The immersion in boiling water can allow for rapid heat transfer from the water to the polymerization solution contained in the tubing. The selection of the tubing can impart microcatheter or catheter compatibility.

In some embodiments, polymer filaments can be sized to deploy, and optionally reposition, through microcatheters with inner diameters ranging from about 0.006 inches to about 0.045 inches or from about 0.006 inches to about 0.028 inches. In another embodiment, polymer filaments can be sized to deploy, and optionally reposition, through 2 Fr, 3 Fr, 4 Fr, 5 Fr, 6 Fr, 7 Fr, 8 Fr, 9 Fr, 10 Fr, and larger catheters.

For delivery through some microcatheters, tubing diameters can range from about 0.006 inches to about 0.025 inches. For delivery through some 4 Fr, 5 Fr, 6 Fr, 7 Fr, and 8 Fr catheters, tubing diameters from about 0.025 inches to about 0.080 inches can be utilized. In one embodiment, the tubing may be made from HYTREL® (DuPont, Wilmington, Del.). The HYTREL® tubing can be dissolved in and/or by solvents, facilitating removal of the tube around the polymer hydrogel. Some hydrogel filament shapes are illustrated in FIGS. 1 and 2. FIG. 1 illustrates a cylindrical, circular or round filament 100 in a dried, straight state or configuration. FIG. 2 illustrates trapezoidal filament 200 in a dried, straight state or configuration.

FIG. 3 illustrates one method of how a hydrogel coil can be attained. If filament 200 is wrapped around a mandrel 300 prior to polymerization of the polymerization solution, the resulting polymer can maintain the shape of filament 200 around mandrel 300 or at least retain a memory of the shape. Using this technique, helical, tornado, and complex shapes can be imparted to the hydrogel filament. When the tubing is wrapped around a mandrel, the use of trapezoidal or oval tubing may be preferred. After wrapping around the mandrel, the oval shape of the tubing can be rounded and the resulting hydrogel filament can have a round shape.

Using HYTREL® tubing, the hydrogel filament can be recovered by incubating the tubing in a solution of 20% w/w phenol in chloroform followed by washing in chloroform and ethanol. After the hydrogel filament has been washed, it can be dried, and a dried hydrogel filament may be produced. The length of a dried filament can range from about 0.01 cm to about 1,000 cm, about 0.1 cm to about 500 cm, about 0.25 cm to about 250 cm, about 0.5 cm to about 100 cm, or any length or range of lengths within those listed. The diameter of a filament can range from about 0.05 inches to about 0.1 inches, or any diameter within this range.

Once a filament has been synthesized and treated to produce the desired properties it can be loaded into an introducer device that facilitates clinical use. If a repositionable device is desired, a length of filament may be inserted into a tube slightly larger its diameter. This can straighten the secondary shape of the filament.

Further, as illustrated in FIGS. 4A and 4B, filament 400 can be attached to a coupler 402. Coupler 402 is further illustrated in various views in FIGS. 5A-5C. As is illustrated in FIG. 4B, the outer diameter 404 of filament 400 can be slightly smaller than or about the same size as the inner diameter 406 of first end 408 of coupler 402.

Coupler 402 can be further attached to an insertion filament 410 that is attached to second end 412 of coupler 402. Again, the outer diameter 414 of insertion filament 410 can be slightly smaller than or about the same size as the inner diameter 416 of second end 412 of coupler 402. Insertion filament 410 can be attached to coupler 402 by gluing, soldering, smashing, flaring, knotting or the like or a combination thereof. For example, as illustrated in FIG. 4B, insertion filament 410 can be knotted 418 within large chamber 420. As long as the knotting 418 is larger than inner diameter 416, then insertion filament 410 cannot detach from coupler 402. A glue 422 can further be used to hold knotting 418 in place and/or the attach filament 400 to coupler 402.

Inner diameter 406 can be sized appropriate for a given filament outer diameter. For example, inner diameter 406 can be about 0.010 inches, about 0.012 inches, about 0.0150 inches, about 0.0155 inches, about 0.0145 inches, or about 0.0120 inches, about 0.0125 inches, about 0.05 inches, about 0.10 inches, or about 0.15 inches.

Inner diameter 416 can be sized appropriate for an insertion filament. For example, inner diameter 416 can be about 0.003, about 0.004 inches, about 0.005 inches or about 0.006 inches.

Coupler 402 can be formed of a plastic or other polymeric material such as, but not limited to rubber, synthetic rubber, silicone polymers, thermoplastics, thermosets, polyolefins, polyisobutylene, acrylic polymers, ethylene-co-vinylacetate, polybutylmethacrylate, vinyl halide polymers (for example, polyvinyl chloride), polyvinyl ethers (for example, polyvinyl methyl ether), polyvinylidene halides, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics, polyvinyl esters, acrylonitrile-styrene copolymers, ABS resins, ethylene-vinyl acetate copolymers, polyamides (for example, Nylon 66 and polycaprolactam), alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, polytetrafluoroethylene (for example, Teflon) and combinations thereof. In one embodiment, a coupler is made of poly (ether-ether-ketone).

In some embodiments, a coupler can also be formed of metal such as, but not limited to aluminum, titanium, zinc, platinum, tantalum, copper, nickel, rhodium, gold, silver, pal-

adium, chromium, iron, indium, ruthenium, osmium, tin, iridium, or combinations and alloys thereof. In some embodiments, a metal is not used if it interferes with imaging of the insertion procedure.

The glue 422 can be any glue that can hold knotting 418 in place and/or attach filament 400 without prematurely severing. The glue can include acrylates, cyanoacrylates, silicones, rubbers, polyurethanes, and combinations thereof. In one embodiment, the glue can be a UV curing glue. In another embodiment, the glue can be acrylate based.

In one embodiment, insertion filament can be fed through second end 412 of coupler 402 and tied into a knot. Then, a UV curable glue is applied over the knot and a filament is inserted until it touches the glue. A UV light can be applied to cure the glue over the knot and against the filament securing all together.

Subsequently, the coupler may be attached to a pusher, packaged, and sterilized. Upon receipt, the physician introduces the filament into a microcatheter or catheter and can then push it through the microcatheter or catheter to the embolization site. The filament can be advanced and withdrawn until the physician is satisfied with its position. Then the filament can then be detached from the pusher.

If a pushable device is desired, a dried hydrogel filament can be loaded into an introducer, packaged in a suitable pouch, and sterilized. Upon receipt, the physician transfers the filament from the introducer to a microcatheter or catheter using a guide wire or stylet. The dried hydrogel filament can then be pushed through the microcatheter or catheter and into the embolization site using a guide wire.

EXAMPLE 1

Preparation of Ethoxylated Trimethylolpropane Triacrylamide

First, 120 g of ethoxylated trimethylolpropane (TMP) 730 was dried by azeotropic distillation with 900 mL of toluene. Then, 82.4 mL of triethylamine was added with 46.8 mL of mesyl chloride and stirred for 12 hours. The solution was then filtered to remove any salt and the solvent evaporated. The resulting product was added to 600 mL of acetonitrile and 1500 mL of 25% ammonia hydroxide and stirred for 3 days. All but 200 mL of water was evaporated and the pH was adjusted to 13 with NaOH. The solution was extracted with dichloromethane, dried over magnesium sulfate, filtered and the solvent evaporated. The resulting ethoxylated trimethylolpropane amine was re-dissolved in 800 mL of dichloromethane and cooled in an ice bath. Then, 78 g of sodium carbonate was added along with 42 mL of acryloyl chloride and stirred for 18 hours. The solution was filtered to remove salt and the solvent evaporated. The resulting ethoxylated trimethylolpropane triacrylamide was then purified over a silica column.

EXAMPLE 2

Preparation of Hydrogel Filament—Fluoroscopy

To prepare a hydrogel filament visible under fluoroscopy, 10.8 g of ethoxylated trimethylolpropane triacrylamide from Example 1, 0.75 g 2-hydroxyethyl methacrylate, 2.4 g N-tert-butylacrylamide, 0.21 g methylenebisacrylamide and 0.14 g 2,2'-azobisisobutyronitrile were dissolved in 7.5 g of isopropyl alcohol. The solution was filtered through a 0.2 micron filter. To 18.2 g of the solution, 21.3 g of barium sulfate was added. The solution was sparged with argon for 10

11

min before injection into oval HYTREL® tubing wrapped around a mandrel. The tubes were heat sealed at both ends and placed in a 100° C. water bath for 1 hour, then overnight in an 80° C. oven to polymerize the solution.

The resulting hydrogel was removed by dissolving the tubing in a solution of 20% phenol in chloroform. After the tubing was removed, the phenol solution was exchanged with chloroform and washed for 1 hr. After 1 hr, the chloroform was exchanged and the hydrogel washed for another 1 hr. The chloroform was removed and the hydrogel dried in a vacuum oven for 2 hr at 50° C. To remove any unreacted monomers, the hydrogel was placed in ethanol for 12 hr. After 12 hr, the ethanol was exchanged and washed for 2 hr. After 2 hr, the ethanol was exchanged and the hydrogel washed for another 2 hr. The ethanol was removed and hydrogel dried in a vacuum oven for 12 hr.

EXAMPLE 3

Preparation of Hydrogel Filament Device

The hydrogel filament of Example 2 can be attached to a V-TRAK® (MicroVention Terumo, Inc., Tustin, Calif.). To attach the hydrogel to a V-TRAK® pusher, a section of 0.0022 inch polyolefin thread was threaded through a coupler. The coupler consisted of a PEEK cylinder hollowed out on one end to accept the hydrogel filament and a through hole. The polyolefin thread was tied into a knot such that it could not be pulled back through. The hydrogel was glued into the coupler on top of the knot using adhesive. The other end of the polyolefin thread was threaded into a V-TRAK® pusher and tied.

EXAMPLE 4

In Vivo Evaluation of Hydrogel Filament Device

Twelve surgically created rabbit bifurcation aneurysms were embolized with radiopaque polymer filaments. The aneurysm width, length, and neck ranged from 1.7 to 11.8 mm. Under fluoroscopic guidance, a microcatheter (Headway®, MicroVention Terumo, Inc., Tustin, Calif.) was placed inside the aneurysm sac. Several radiopaque hydrogel filaments were deployed inside the aneurysm sac. Six of the aneurysms were embolized as completely as possible while the remaining 6 were incompletely embolized to ensure blood filling in the neck. At four and 13 weeks post-embolization, stable occlusion of all 12 aneurysms was demonstrated by angiography. The aneurysms were harvested and histologically processed. The aneurysm sacs were filled with the radiopaque hydrogel filaments and mixtures of fibrovascular tissue and unorganized thrombus. The necks were almost completely to completely traversed with an endothelialized neointima. Inflammation was minimal to mild. These results illustrated that the radiopaque hydrogel filaments can be deployed into experimental aneurysms and elicit a foreign body response consistent with other embolic devices.

CT Evaluation of Hydrogel Filament Device

Twelve surgically created rabbit bifurcation aneurysms embolized with radiopaque polymer filaments underwent CT angiography follow up at 4 and 13 weeks post-embolization. CTA was performed using a 10-multisectional helical CT machine (Brilliance 10; Philips Healthcare). Contrast was administered through a cannula in the ear vein. When imaged, the beam-hardening artifacts of the hydrogel filaments were

12

greatly reduced compared to previously imaged platinum coils. The embolus, individual coils, and neck remnants were visible with CTA. CTA imaging can be suitable for determining if re-treatment is necessary for aneurysms embolized with radiopaque hydrogel filaments.

MR Evaluation of Hydrogel Filament Device

Twelve surgically created rabbit bifurcation aneurysms embolized with radiopaque polymer filaments underwent MR angiography follow up at 4 and 13 weeks post-embolization. The aneurysms were imaged with a 3T scanner (Magnetom Trio; Siemens) using a 3D time-of-flight sequence. Only the neck remnants were visible with MRA, similar to platinum coils. MRA imaging can be suitable for determining if re-treatment is necessary for aneurysms embolized with radiopaque hydrogel filaments.

EXAMPLE 5

In Vitro Evaluation of the Bending Resistance of the Hydrogel Filament

The bending resistance of the hydrogel filaments of the formulation in Example 2 was measured. The hydrogels were prepared in tubing of various diameters. Measurements were obtained using a Gurley 4171ET tubular sample stiffness tester with a 5 g counterweight attached to its measuring vane. The sample length was one inch. The bending resistance was measured in the dry state as well as after 30 seconds of hydration with 0.9% saline. The average of three to five replicates each are summarized in the following table.

Sample	Measured Resistance (mg) Dry	Measured Resistance (mg) Hydrated for 30 seconds
0.0055"	0.49 ± 0.27	0.28 ± 0.12
0.010"	1.11 ± 0.23	0.28 ± 0.07
0.017"	6.67 ± 0.60	4.73 ± 0.88
0.018"	9.04 ± 0.16	7.78 ± 0.23
0.020"	10.56 ± 0.79	8.62 ± 0.72
0.025"	19.07 ± 0.98	17.38 ± 1.17
0.030"	36.39 ± 1.53	29.40 ± 1.90
0.035"	63.68 ± 1.46	59.10 ± 4.74
0.040"	128.21 ± 0.79	121.58 ± 1.31
0.080"	1,021.20 ± 69.62	860.25 ± 54.76

The results illustrate the range of bending resistances achievable.

EXAMPLE 6

In Vitro Evaluation of the Ultimate Tensile Strength of the Hydrogel Filament

The ultimate tensile strength of hydrogel filaments prepared in tubings of various diameters of the formulation in Example 2 were obtained using an Instron 5543. The ultimate tensile strength was measured in the dry state as well as after one hour of hydration with 0.9% saline (full hydration). The average of three to five replicates each are summarized in the following table.

Sample	Tensile Strength (lbf) Dry	Tensile Strength (lbf) Hydrated
0.0055"	0.033 ± 0.002	0.009 ± 0.002
0.010"	0.072 ± 0.010	0.039 ± 0.006

-continued

Sample	Tensile Strength (lbf) Dry	Tensile Strength (lbf) Hydrated
0.017"	0.247 ± 0.024	0.138 ± 0.014
0.018"	0.298 ± 0.006	0.132 ± 0.021
0.020"	0.268 ± 0.030	0.134 ± 0.037
0.025"	0.443 ± 0.060	0.225 ± 0.016
0.030"	0.577 ± 0.055	0.271 ± 0.057
0.035"	0.415 ± 0.101	0.300 ± 0.097
0.040"	1.250 ± 0.136	0.513 ± 0.093
0.080"	2.572 ± 0.576	1.055 ± 0.200

The results illustrate the range of ultimate tensile strengths achievable.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

The terms "a," "an," "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

Groupings of alternative elements or embodiments of the invention disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

Certain embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these

described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

In closing, it is to be understood that the embodiments of the invention disclosed herein are illustrative of the principles of the present invention. Other modifications that may be employed are within the scope of the invention. Thus, by way of example, but not of limitation, alternative configurations of the present invention may be utilized in accordance with the teachings herein. Accordingly, the present invention is not limited to that precisely as shown and described.

We claim:

1. A hydrogel for implantation comprising: a shapeable polymeric filament formed from a combination of precursors comprising trimethylolpropane ethoxylate triacrylamide, at least one ethylenically unsaturated acrylamide monomer, at least one ethylenically unsaturated methacrylate monomer, and a crosslinker; and the hydrogel further comprises at least one visualization agent; wherein the hydrogel includes no metal support members.

2. The hydrogel according to claim 1, having reduced beam hardening artifacts when imaged using computed tomography.

3. The hydrogel according to claim 1, wherein the at least one visualization agent is selected from metallic powders, gadolinium, superparamagnetic iron oxide particles, barium sulfate or a combination thereof.

4. The hydrogel according to claim 1, wherein the polymeric filament has a diameter of less than about 0.03 inches.

5. The hydrogel according to claim 1, wherein the polymeric filament is substantially non-resorbable.

6. The hydrogel according to claim 1, wherein the polymeric filament is biodegradable.

7. The hydrogel according to claim 1, wherein the at least one ethylenically unsaturated acrylamide monomer is t-butyl acrylamide.

8. The hydrogel according to claim 1, wherein the at least one ethylenically unsaturated methacrylate monomer is hydroxyethyl methacrylate.

9. The hydrogel according to claim 1, wherein the ethylenically unsaturated acrylamide monomer and ethylenically unsaturated methacrylate monomer are a combination of hydroxyethyl methacrylate and t-butyl acrylamide.

10. The hydrogel according to claim 1, wherein the molecular weight of the trimethylolpropane ethoxylate triacrylamide is about 900 g/mol.

11. The hydrogel according to claim 1, wherein the crosslinker is N,N'-methylenebisacrylamide.

12. A method of forming a hydrogel comprising:

- preparing a polymerization solution comprising trimethylolpropane ethoxylate triacrylamide; at least one ethylenically unsaturated monomer; and at least one visualization element in a solvent;
- polymerizing the polymerization solution to create a polymerized hydrogel; and
- drying the polymerized hydrogel thereby forming the hydrogel.

15

13. The method according to claim 12, wherein step b further comprises polymerizing the polymerization solution in a tube thereby creating a polymerized hydrogel filament having the shape of the internal volume of the tube.

14. The method according to claim 12, wherein the solvent is selected from isopropanol, ethanol, water, dichloromethane, and acetone.

15. The method according to claim 12, wherein the at least one ethylenically unsaturated monomer is t-butyl acrylamide.

16. The method according to claim 12, wherein the at least one ethylenically unsaturated monomer is hydroxyethyl methacrylate.

17. The method according to claim 12, wherein the ethylenically unsaturated monomer is a combination of hydroxyethyl methacrylate and t-butyl acrylamide.

18. The method according to claim 12, wherein the polymerization solution further comprises a multifunctional cross-linker.

19. The method according to claim 12, wherein the cross-linker is N,N'-methylenebisacrylamide.

16

20. A method of forming a hydrogel comprising: drying a hydrogel filament, wherein the hydrogel filament is polymerized from a polymerization solution comprising trimethylolpropane ethoxylate triacrylamide macromer with a molecular weight of about 900 g/mol; at least one ethylenically unsaturated monomer; and at least one visualization element in a solvent.

21. A hydrogel filament consisting essentially of about 27% w/w trimethylolpropane ethoxylate triacrylamide with a molecular weight of about 900 g/mol, about 6% w/w t-butyl acrylamide, about 2% hydroxyethyl methacrylate, about 0.5% w/w N,N-methylenebisacrylamide, about 64% barium sulfate, and about 0.5% 2,2'-azobisisobutyronitrile.

22. A hydrogel filament consisting essentially of about 30% w/w trimethylolpropane ethoxylate triacrylamide with a molecular weight of about 900 g/mol, about 6% w/w t-butyl acrylamide, about 2% hydroxyethyl methacrylate, about 0.75% w/w N,N-methylenebisacrylamide, about 48% barium sulfate, and about 0.5% 2,2'-azobisisobutyronitrile.

* * * * *